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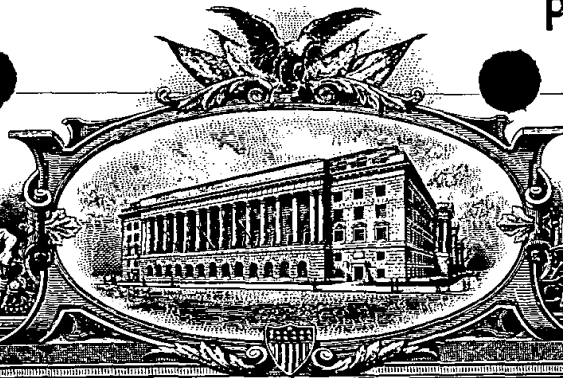
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APPLICATION NUMBER: 09/206,601

FILING DATE: December 07, 1998

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BPC089

TO THE ASSISTANT COMMISSIONER FOR PATENTS

Transmitted herewith for filing under 35 U.S.C. 111 and 37 C.F.R. 1.53 is the patent application of:

Z. X. Dong

For: ANALOGUES OF GLP-1

Enclosed are:

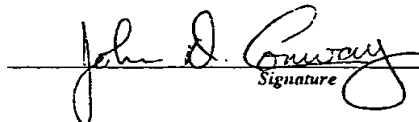
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Dated: December 7, 1998


SignatureJohn D. Conway
Reg. No. 39,150

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Patent
Attorney Docket No.: BPC089

**NON-PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(b)(1)**

09206501-12098
864027-70990260

TITLE: ANALOGUES OF GLP-1

APPLICANT: ZHENG XIN DONG

EXPRESS MAIL LABEL NO. EE788788332US

ANALOGUES OF GLP-1

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Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

10 Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J.M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma
15 insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying
20 (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak,
25 M.K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulphonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose
30 concentration (Holz, G.G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against severe hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently
35 influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C,

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Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefebvre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diabetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

10 GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

15 Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),
(R²R³)-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-
A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R¹,

(I)

20 wherein

A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, or deleted, provided that when A⁷ is Ura, Paa or Pta, then R² and R³ are deleted;

A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;

25 A¹⁰ is Gly, Acc or Aib;

A¹¹ is Thr or Ser;

A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X¹-Phe;

A¹³ is Thr or Ser;

A¹⁴ is Ser or Aib;

30 A¹⁵ is Asp or Glu;

A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A¹⁷ is Ser or Thr;

A¹⁸ is Ser or Thr;

A¹⁹ is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal or X¹-Phe;

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A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;

A²¹ is Glu or Asp;

A²² is Gly, Acc, β-Ala or Aib;

A²³ is Gln, Asp, Asn or Glu;

5 A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)₆-X³)-C(O);

A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)₆-X³)-C(O);

A²⁷ is Glu or Asp;

10 A²⁸ is Phe, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;

A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A³⁰ is Ala, Aib or Acc;

A³¹ is Trp, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe or Ala;

15 A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu or X¹-Phe;

A³⁴ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)₆-X³)-C(O);

A³⁵ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc or a D-amino acid;

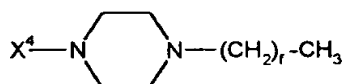
A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Om, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)₆-X³)-C(O) or deleted;

20 A³⁷ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc, Ado, a D-amino acid or deleted;

A³⁸ is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Om, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)₆-X³)-C(O) or deleted;

25 X¹ for each occurrence is independently selected from the group consisting of (C₁-C₆)alkyl, OH and halo;

R¹ is OH, NH₂, (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z, wherein X² is a (C₁-C₃₀)hydrocarbon moiety, and Z is H, OH, CO₂H or CONH₂;

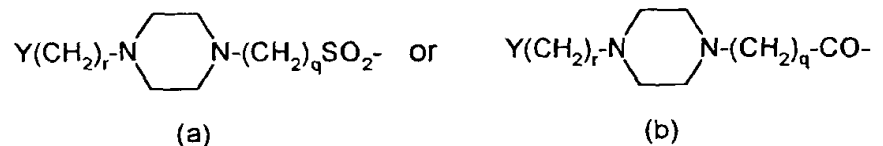


X³ is or -C(O)-NHR¹², wherein X⁴ for each occurrence is independently -C(O)-, -NH-C(O)- or -CH₂-, and f for each occurrence is independently an integer from 1 to 29;

30 each of R² and R³ is, independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-

C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and

hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is $(\text{CH}_3)_2\text{-N}-\overset{\uparrow}{\text{C}}=\overset{+}{\text{N}}(\text{CH}_3)_2$, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, C(O)X⁵,



5 where Y is H, OH or NH₂; r is 0 to 4; q is 0 to 4; X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl or hydroxynaphthyl(C₁-C₃₀)alkyl;

e for each occurrence is independently an integer from 1 to 4;

10 m for each occurrence is independently an integer from 5-24;

n for each occurrence is independently an integer from 1-5;

R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



15 C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or (C₁-C₃₀)alkyl; and

R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

- 20 (i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;
- (ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;
- (iii) a compound of formula (I) is not [Arg^{26,34}, Lys³⁸]hGLP-1(7-38)-E, [Lys²⁶(N^f-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys³⁴(N^f-alkanoyl)]hGLP-1(7-36, -37 or -38)-E,
- 25 [Lys^{26,34}-bis(N^f-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Arg²⁶, Lys³⁴(N^f-alkanoyl)]hGLP-1(8-

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36, -37 or -38)-E, [Arg^{26,34}, Lys³⁶(N^f-alkanoyl)]hGLP-1(7-36, -37 or -38)-E or [Arg^{26,34}, Lys³⁸(N^f-alkanoyl)]hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, -37 or -38)-OH, Z-hGLP-1(7-36, -37 or -38)-NH₂, where Z is selected from the group consisting of

5 (a) [Arg²⁶], [Arg³⁴], [Arg^{26,34}], [Lys³⁶], [Arg²⁶, Lys³⁶], [Arg³⁴, Lys³⁶], [D-Lys³⁶], [Arg³⁶], [D-Arg³⁶], [Arg^{26,34}, Lys³⁶] or [Arg^{26,36}, Lys³⁴];

(b) [Asp²¹];

(c) at least one of [Aib⁸], [D-Ala⁸] and [Asp⁹]; and

(d) [Tyr⁷], [N-acyl-His⁷], [N-alkyl-His⁷], [N-acyl-D-His⁷] or [N-alkyl-D-His⁷];

10 (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36 or -37), [Glu¹⁵]hGLP-1(7-36 or -37), [Asp²¹]hGLP-1(7-36 or -37) or [Phe³¹]hGLP-1(7-36 or -37).

A preferred group of compounds of the immediately foregoing compound, is where

15 A¹¹ is Thr; A¹³ is Thr; A¹⁵ is Asp; A¹⁷ is Ser; A¹⁸ is Ser; A²¹ is Glu; A²³ is Gln or Glu; A²⁷ is Glu; and A³¹ is Trp; or a pharmaceutically acceptable salt thereof.

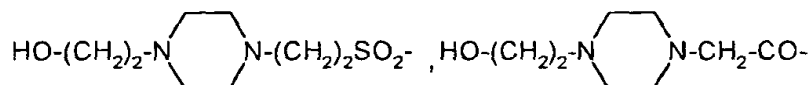
A preferred group of compounds of the immediately foregoing group of compounds is where A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, Acc or Aib; A¹⁹ is Tyr; A²⁰ is Leu, Acc or Cha; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Om, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O); A²⁸ is Phe; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val or Acc; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² 25 is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

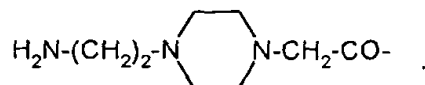
A preferred group of compounds of the immediately foregoing group of compounds 30 is where X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R¹ is OH or NH₂, or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,

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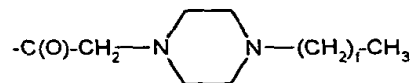


or



A preferred compound of the formula (I) is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R¹ is OH or NH₂; R¹⁰ is (C₁-C₃₀)acyl, (C₁-

$-\text{C}(\text{O})-\text{CH}_2-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{N}-(\text{CH}_2)_r\text{CH}_3$ C₃₀)alkylsulfonyl or , and R¹¹ is H; or a pharmaceutically acceptable salt thereof. More preferred of the foregoing compounds is



10 where R¹⁰ is (C₄-C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or , or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula [Aib^{8,35}]hGLP-1(7-36)NH₂,

[(N^α-HEPES-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,

15 [(N^α-HEPA-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,

[Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,

[Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,

20 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine))]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂,

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[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl),β-Ala³⁷]hGLP-1(7-37)-OH or
[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH, or a pharmaceutically
acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of
5 the formula

[Aib^{8,35}]hGLP-1(7-36)NH₂,

[Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,

[Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,

[Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,

10 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂, or

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl),β-Ala³⁷]hGLP-1(7-37)-OH, or a pharmaceutically
acceptable salt thereof.

Another more preferred compound of formula (I) is each of the compounds that are
specifically enumerated hereinbelow in the Examples section of the present disclosure, or a
15 pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition
comprising an effective amount of a compound of formula (I) as defined hereinabove or a
pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or
diluent.

20 In yet another aspect, the present invention provides a method of eliciting an agonist
effect from a GLP-1 receptor in a subject in need thereof which comprises administering to
said subject an effective amount of a compound of formula (I) as defined hereinabove or a
pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a method of treating a disease
25 selected from the group consisting of Type I diabetes, Type II diabetes, obesity,
glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis,
central nervous system disease, restenosis and neurodegenerative disease, in a subject in
need thereof which comprises administering to said subject an effective amount of a
compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt
30 thereof. A preferred method of the immediately foregoing method is where the disease
being treated is Type I diabetes or Type II diabetes.

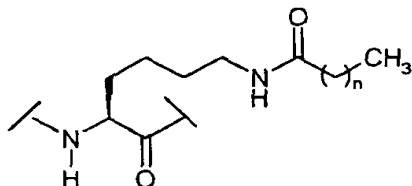
With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino
acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side

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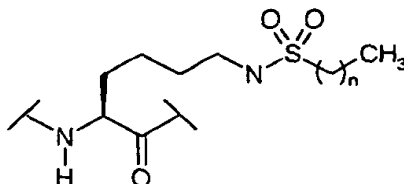
chain of an amino acid (e.g., CH₃ for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R²R³)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R² and R³ are as defined above, except when A⁷ is Ura, Paa or Pta, in which case R² and R³ are not present since Ura, Paa and Pta are considered here as des-amino amino acids. Amp, β-Nal, Nle, Cha, 3-Pal, 4-Pal and Aib are the abbreviations of the following α-amino acids: 4-amino-phenylalanine, β-(2-naphthyl)alanine, norleucine, cyclohexylalanine, β-(3-pyridinyl)alanine, β-(4-pyridinyl)alanine and α-aminoisobutyric acid, respectively. Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α-aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α-aminoisobutyric acid; β-Ala is β-alanine; Gaba is γ-aminobutyric acid; Ava is 5-aminovaleric acid; Ado is 12-aminododecanoic acid and Aic is 2-aminoindane-2-carboxylic acid.

What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c). In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX⁵ stands for -C=O-X⁵. Examples of -C=O-X⁵ include, but are not limited to, acetyl and phenylpropionyl.

What is meant by Lys(N^e-alkanoyl) is represented by the following structure:



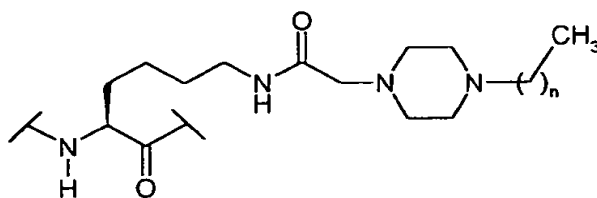
. What is meant by Lys(N^e-alkylsulfonyl) is represented



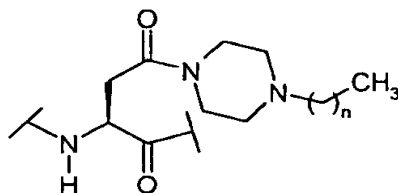
25 by the following structure:

. What is meant by Lys(N^e-

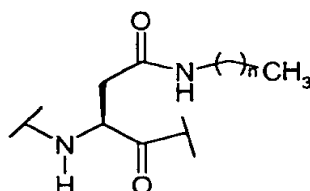
(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following



structure: . What is meant by Asp(1-(4-alkyl-piperazine)) is represented by the following



structure: . What is meant by Asp(1-alkylamino) is



5 represented by the following structure: . The variable n in the foregoing structures is 1-30.

The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2CIZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl, OcHex for O-cyclohexyl, Fmoc for 9-fluorenylmethoxycarbonyl, HOBt for N-hydroxybenzotriazole and PAM resin for 4-hydroxymethylphenylacetamidomethyl resin.

The term "halo" encompasses fluoro, chloro, bromo and iodo.

The term "(C₁-C₁₂)hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there are C₂-C₁₂.

A peptide of this invention is also denoted herein by another format, e.g., [A5c⁸]hGLP-1(7-36)NH₂, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., A5c⁸ for Ala⁸ in hGLP-1). The abbreviation GLP-1 means

glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res., 40, 1992, pp. 333-342. The designation "NH₂" in hGLP-1(7-36)NH₂ indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid. In hGLP-1(7-38), residues in positions 37 and 38 are Gly and Arg, respectively.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R² and R³ of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C₁-C₃₀)alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C₁-C₃₀)hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE¹, may be attached by coupling the free acid, e.g., E¹COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBt.

When R¹ is NH-X²-CH₂-Z (Z=CONH₂), the synthesis of the peptide starts with BocHN-X²-CH₂-COOH which is coupled to the MBHA resin. If R¹ is NH-X²-CH₂-COOH (Z=COOH) the synthesis of the peptide starts with Boc-HN-X²-CH₂-COOH which is coupled to PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X²-COOH, HBTU and HOBt and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

The protected amino acid 1-[N-tert-butoxycarbonyl-amino]-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic

layer was separated. The aqueous layer was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous MgSO_4 , filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. For the synthesis of $[\text{Tma-His}^7]\text{hGLP-1(7-36)NH}_2$, HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF are used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., $(\text{C}_1\text{-C}_{30})$ alkyl, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., $(\text{C}_1\text{-C}_{30})$ hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^1 , can be attached by coupling the free acid, e.g., X^1COOH , to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37°C in a humidified atmosphere of 5% CO_2 /95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10

min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM MgCl₂, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM [¹²⁵I]GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound [¹²⁵I]GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total [¹²⁵I]GLP-1(7-36) bound minus that bound in the presence of 1000 nM GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous [See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536]. Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes,

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obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis and neurodegenerative diseases. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of 1×10^{-7} to 200 mg/kg/day, preferably 1×10^{-4} to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous

solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, 5 by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which 10 may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release 15 composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a 20 bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as 25 a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are 30 incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

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The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

5

Example 1

[Aib^{8,35}]hGLP-1(7-36)NH₂

10 The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-Methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2CIZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2CIZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

15 At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side of the chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The partially-deprotected peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

25 The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C₁₈ column (Nest Group, Southborough, MA). The column was eluted with a linear gradient

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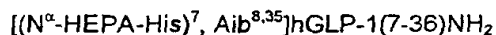
(20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

Example 2



The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after synthesis of the peptide $[\text{His}^7, \text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min. After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 3



The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making $[(N^{\alpha}\text{-HEPES-His})^7, \text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Example 4



The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) = 3325.7, calculated MW = 3325.8, purity = 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of $[\text{Aib}^{8,35}]\text{hGLP-1(7-36)NH}_2$ in Example 1 above, but using the appropriate protected amino

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acids depending on the desired peptide.

Example 5



5 The Boc amino acids used were the same as those in the synthesis of
[Aib^{8,35}]hGLP-1(7-36)NH₂ described in Example 1 except that Fmoc-Lys(Boc)-OH was used
in this example. The first amino acid residue was coupled to the resin manually on a
shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To
the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the
10 solution was then added 0.2 mmol of MBHA resin (substitution = 0.93 mmol/g). The mixture
was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for
2x2 min to remove the Boc protecting group. The resin was washed with DMF. Myristic acid
(2.5 mmol) was pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for
2 min and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin
15 was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the
Fmoc protecting group. The resin was washed with DMF and transferred to the reaction
vessel of the peptide synthesizer. The synthesis and purification procedures of the
remainder of the peptide were the same as those in the synthesis of [Aib^{8,35}]hGLP-1(7-
36)NH₂ in Example 1. 43.1 mg of the title compound was obtained as a white solid. Purity
20 was 98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis
gave the molecular weight at 3577.7 in agreement with the calculated molecular weight
3578.7.

Examples 6-8

Examples 6-8 were synthesized substantially according to the procedure described
for Example 5 using the appropriate protected amino acid and the appropriate acid in place
25 of the Myristic acid used in Example 5.

Example 6: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂; Yield = 89.6 mg;
MS(ES) = 3577.2, Calculated MW = 3578.7; Purity 96%.

Example 7: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂; Yield = 63.3 mg;
MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

30 Example 8: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂; Yield = 57.4 mg;
MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

The syntheses of other compounds of the present invention containing Lys(N^ε-
alkanoyl) residue can be carried out in an analogous manner to the procedure described for
Example 8, [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂. Fmoc-Lys(Boc)-OH

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amino acid is used for the residue of Lys(N^ε-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N^ε-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-alkanoyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 9



The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin(substitution = 0.93 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N^ε-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-alkylsulfonyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N^ε-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate alkylsulfonyl chloride can be obtained from Lancaster Synthesis Inc., Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

Example 10

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))hGLP-1(7-36)NH₂

5 The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. The 2-bromoacetic acid
10 (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures of the remainder of the peptide are the same as the procedures described for Example 1.

20 The syntheses of other compounds of the present invention containing Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is
25 used for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 11

30 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine))hGLP-1(7-36)NH₂

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36 and Boc-Asp(OcHex)-OH is used at position 15. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N

HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min 0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures for the remainder of the peptide are the same as those for the synthesis of Example 1.

The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used for the residue of Lys(N^ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is assembled on the resin on the peptide synthesizer first.

Example 12

[Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂

The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.93 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min 0.6 mmol of 1-tetradecaneamine is added to the reaction mixture and the mixture is shaken for about 1 hr.

The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The synthesis and purification procedures for the remainder of the peptide of this example are the same as those described for the synthesis of Example 1.

The syntheses of other compounds of the present invention containing Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

Example 13

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH

The Boc amino acids used are the same as those in the synthesis of [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂ (Example 5). 270 mg of Boc-β-Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc-β-Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

Example 14

[Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH

The Boc amino acids to be used are the same as those in the synthesis of [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂ (Example 5). Fmoc-Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBT (2.0 mmol and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5.

The syntheses of other analogs of hGLP-1(7-36)-OH, hGLP-1(7-37)-OH and hGLP-1(7-38)-OH of the instant application, which contain Lys(N^ε-alkanoyl) residue, can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^ε-alkanoyl) in the peptide, while Boc-Lys(2CIZ)-OH amino acid is used for the residue of Lys.

The following examples can be made according to the appropriate procedures described hereinabove.

- Example 15: [Aib³⁵]hGLP-1(7-36)NH₂
- Example 16: [β-Ala³⁵]hGLP-1(7-36)NH₂
- 10 Example 17: [(N^α-Me-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂
- Example 18: [(N^α-Me-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 19: [(N^α-Me-His)⁷, Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂
- Example 20: [(N^α-Me-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 21: [Aib⁸, A6c³⁵]hGLP-1(7-36)NH₂
- 15 Example 22: [Aib⁸, A5c³⁵]hGLP-1(7-36)NH₂
- Example 23: [Aib⁸, D-Ala³⁵]hGLP-1(7-36)NH₂
- Example 24: [Aib^{8,35}, A6c³²]hGLP-1(7-36)NH₂
- Example 25: [Aib^{8,35}, A5c³²]hGLP-1(7-36)NH₂
- Example 26: [Aib^{8,35}, Glu²³]hGLP-1(7-36)NH₂
- 20 Example 27: [Aib^{8,24,35}]hGLP-1(7-36)NH₂
- Example 28: [Aib^{8,30,35}]hGLP-1(7-36)NH₂
- Example 29: [Aib^{8,25,35}]hGLP-1(7-36)NH₂
- Example 30: [Aib^{8,35}, A6c^{16,20}]hGLP-1(7-36)NH₂
- Example 31: [Aib^{8,35}, A6c^{16,29,32}]hGLP-1(7-36)NH₂
- 25 Example 32: [Aib^{8,35}, A6c^{20,32}]hGLP-1(7-36)NH₂
- Example 33: [Aib^{8,35}, A6c²⁰]hGLP-1(7-36)NH₂
- Example 34: [Aib^{8,35}, Lys²⁵]hGLP-1(7-36)NH₂
- Example 35: [Aib^{8,24,35}, A6c²⁰]hGLP-1(7-36)NH₂
- Example 36: [Aib^{8,35}, A6c^{29,32}]hGLP-1(7-36)NH₂
- 30 Example 37: [Aib^{8,24,35}, A6c^{29,32}]hGLP-1(7-36)NH₂
- Example 38: [Aib^{8,35}, A6c¹²]hGLP-1(7-36)NH₂
- Example 39: [Aib^{8,35}, Cha²⁰]hGLP-1(7-36)NH₂
- Example 40: [Aib^{8,35}, A6c³³]hGLP-1(7-36)NH₂
- Example 41: [Aib^{8,35}, A6c^{20,32}]hGLP-1(7-36)NH₂

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- Example 42: [Aib⁸, A6c^{16,20}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 43: [Aib^{8,35}, β-Ala²²]hGLP-1(7-36)NH₂
- Example 44: [Aib^{8,22,35}]hGLP-1(7-36)NH₂
- Example 45: [Aib^{8,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- 5 Example 46: [Aib^{8,24,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- Example 47: [Aib^{8,24,25,35}, Glu²³, A6c³²]hGLP-1(7-36)NH₂
- Example 48: [Aib^{8,24,25,35}, A6c^{16,20,32}, Glu²³]hGLP-1(7-36)NH₂
- Example 49: [Aib⁸, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 50: [Aib⁸, A5c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- 10 Example 51: [Aib⁸, Glu²³, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 52: [Aib^{8,24}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 53: [Aib^{8,30}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 54: [Aib^{8,25}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 55: [Aib⁸, A6c^{16,20}, β-Ala³⁵]hGLP-1(7-36)NH₂
- 15 Example 56: [Aib⁸, A6c^{16,29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 57: [Aib⁸, A6c^{20,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 58: [Aib⁸, A6c²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 59: [Aib⁸, Lys²⁵, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 60: [Aib^{8,24}, A6c²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- 20 Example 61: [Aib⁸, A6c^{29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 62: [Aib^{8,24}, A6c^{29,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 63: [Aib⁸, A6c¹², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 64: [Aib⁸, Cha²⁰, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 65: [Aib⁸, A6c³³, β-Ala³⁵]hGLP-1(7-36)NH₂
- 25 Example 66: [Aib⁸, A6c^{20,32}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 67: [Aib⁸, β-Ala^{22,35}]hGLP-1(7-36)NH₂
- Example 68: [Aib^{8,22}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 69: [Aib⁸, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 70: [Aib^{8,24}, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 71: [Aib^{8,24}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 72: [Aib^{8,24,25}, Glu²³, A6c³², β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 73: [Aib^{8,24,25}, A6c^{16,20,32}, Glu²³, β-Ala³⁵]hGLP-1(7-36)NH₂

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- Example 74: [Aib^{8,35}, D-Arg³⁶]hGLP-1(7-36)NH₂
- Example 75: [Aib^{8,35}, D-Lys³⁶]hGLP-1(7-36)NH₂
- Example 76: [Aib⁸, β-Ala³⁵, D-Arg³⁶]hGLP-1(7-36)NH₂
- Example 77: [Aib⁸, β-Ala³⁵, D-Lys³⁶]hGLP-1(7-36)NH₂
- 5 Example 78: [Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂
- Example 79: [Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 80: [Aib^{8,35}, Arg^{25,26,34}]hGLP-1(7-36)NH₂
- Example 81: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 82: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)OH
- 10 Example 83: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
- Example 84: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
- Example 85: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), D-Ala³⁷]hGLP-1(7-37)OH
- Example 86: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
- Example 87: [Aib^{8,35}, Arg^{26,34}, β-Ala³⁷, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
- 15 Example 88: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
- Example 89: [Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)OH
- Example 90: [Aib^{8,37}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-37)OH
- Example 91: [Aib^{8,35}, Arg^{26,34}, Ado³⁷]hGLP-1(7-37)OH
- Example 92: [Aib^{8,35}, Arg^{26,34}, Ado³⁷]hGLP-1(7-37)NH₂
- 20 Example 93: [Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), D-Ala³⁷]hGLP-1(7-37)OH
- Example 94: [Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
- Example 95: [Aib⁸, Arg^{26,34}, β-Ala³⁷, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)OH
- Example 96: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 97: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 25 Example 98: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 99: [Aib⁸, Lys²⁶(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 100: [Aib⁸, Lys²⁶(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 101: [Aib⁸, Lys²⁶(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 102: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- 30 Example 103: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 104: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 105: [Aib^{8,35}, Lys²⁶(N^ε-decanoyl), Arg³⁴]hGLP-1(7-36)NH₂

- Example 106: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 107: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 108: [Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 109: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 5 Example 110: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 111: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 112: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 113: [Aib⁸, Lys²⁶(N^ε-octanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 114: [Aib⁸, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- 10 Example 115: [Aib⁸, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 116: [Aib⁸, Lys²⁶(N^ε-decanoyl), Arg³⁴, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 117: [Aib^{8,35}, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 118: [Aib^{8,35}, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 119: [Aib^{8,35}, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 15 Example 120: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 121: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 122: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 123: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 124: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 125: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 126: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 127: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 128: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 129: [Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 25 Example 130: [Aib^{8,35}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 131: [Aib^{8,35}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 132: [Aib^{8,35}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 133: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 134: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 30 Example 135: [Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 136: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 137: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂

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- Example 138: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 139: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 140: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- Example 141: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- 5 Example 142: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 143: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 144: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- Example 145: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 146: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- 10 Example 147: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 148: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 149: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl)]hGLP-1(7-38)NH₂
- Example 150: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl)]hGLP-1(7-38)NH₂
- Example 151: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂
- 15 Example 152: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-hexadecanoyl)]hGLP-1(7-38)NH₂
- Example 153: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 154: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 155: [Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 156: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 20 Example 157: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 158: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 159: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 160: [Aib⁸, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 161: [Aib⁸, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 25 Example 162: [Aib⁸, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 163: [Aib⁸, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 164: [Aib⁸, Glu²³, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 165: [Aib⁸, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 166: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 167: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 168: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 169: [Aib⁸, Arg²⁶, Lys³⁴(N^ε-decanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂

- Example 170: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 171: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 172: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 173: [Aib⁸, Arg^{25,26}, Lys³⁴(N^ε-decanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
5 Example 174: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-octanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 175: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 176: [Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
Example 177: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 178: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
10 Example 179: [Aib⁸, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 180: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 181: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
Example 182: [Aib⁸, Arg²⁶, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 183: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
15 Example 184: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
Example 185: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 186: [Aib⁸, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
Example 187: [Aib⁸, Lys²⁵, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 188: [Aib⁸, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁵]hGLP-1(7-36)NH₂
20 Example 189: [Aib⁸, Lys²⁵, Arg^{26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 190: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 191: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
Example 192: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 193: [Aib⁸, Arg^{25,26,34}, β-Ala³⁵, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
25 Example 194: [Aib^{8,35}, Lys²⁶(N^ε-octanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
Example 195: [Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
Example 196: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl), A6c³², Arg³⁴]hGLP-1(7-36)NH₂
Example 197: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 198: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
30 Example 199: [Aib^{8,35}, A6c³², Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
Example 200: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
Example 201: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂

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- Example 202: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 203: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 204: [Aib^{8,35}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 205: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 5 Example 206: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 207: [Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 208: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 209: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂
- Example 210: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 10 Example 211: [Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 212: [Aib^{8,24,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 213: [Aib^{8,24,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 214: [Aib^{8,24,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 215: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 15 Example 216: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 217: [Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 218: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 219: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 220: [Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 221: [Aib^{8,24,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 222: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 223: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 224: [Aib^{8,35}, Glu²³, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 225: [Aib^{8,35}, Glu²³, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 25 Example 226: [Aib^{8,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 227: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 228: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 229: [Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 230: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 30 Example 231: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 232: [Aib^{8,35}, Glu²³, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 233: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂

- Example 234: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 235: [Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 236: [Aib^{8,30,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 237: [Aib^{8,30,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- 5 Example 238: [Aib^{8,30,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴]hGLP-1(7-36)NH₂
- Example 239: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 240: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 241: [Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 242: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- 10 Example 243: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 244: [Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 245: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 246: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 247: [Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- 15 Example 248: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 249: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 250: [Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 251: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 252: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- 20 Example 253: [Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 254: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl)]hGLP-1(7-36)NH₂
- Example 255: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂
- Example 256: [Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl)]hGLP-1(7-36)NH₂
- Example 257: [(N^α-HEPES-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- 25 Example 258: [(N^α-HEPES-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 259: [(N^α-HEPES-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 260: [(N^α-HEPA-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- Example 261: [(N^α-HEPA-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 262: [(N^α-HEPA-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
- 30 Example 263: [(N^α-tetradecanoyl-His)⁷, Aib³⁵]hGLP-1(7-36)NH₂
- Example 264: [(N^α-tetradecanoyl-His)⁷, β-Ala³⁵]hGLP-1(7-36)NH₂
- Example 265: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂

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- Example 266: [(N^α-tetradecanoyl-His)⁷, Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂
Example 267: [(N^α-tetradecanoyl-His)⁷, Arg^{26,34}, Aib³⁵]hGLP-1(7-36)NH₂
Example 268: [(N^α-tetradecanoyl-His)⁷, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
Example 269: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{26,34}]hGLP-1(7-36)NH₂
5 Example 270: [(N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
Example 271: [(N^α-tetradecanoyl-His)⁷, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
Example 272: [(N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{25,26,34}]hGLP-1(7-36)NH₂
Example 273: [(N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{25,26,34}, β-Ala³⁵]hGLP-1(7-36)NH₂
Example 274: [Aib^{8,35}, Lys²⁶(N^ε-octanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
10 Example 275: [Aib^{8,35}, Lys²⁶(N^ε-dodecanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
Example 276: [Aib^{8,35}, Lys²⁶(N^ε-hexadecanesulfonyl), Arg³⁴]hGLP-1(7-36)NH₂
Example 277: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanesulfonyl)]hGLP-1(7-36)NH₂
Example 278: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂
Example 279: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanesulfonyl)]hGLP-1(7-36)NH₂
15 Example 280: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanesulfonyl)]hGLP-1(7-36)NH₂
Example 281: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanesulfonyl)]hGLP-1(7-36)NH₂
Example 282: [Aib^{8,35}, Asp²⁶(1-(4-decylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
Example 283: [Aib^{8,35}, Asp²⁶(1-(4-dodecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
Example 284: [Aib^{8,35}, Asp²⁶(1-(4-tetradecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
20 Example 285: [Aib^{8,35}, Asp²⁶(1-(4-hexadecylpiperazine)), Arg³⁴]hGLP-1(7-36)NH₂
Example 286: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
Example 287: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
Example 288: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
Example 289: [Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
25 Example 290: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
Example 291: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
Example 292: [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
Example 293: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
Example 294: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
30 Example 295: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
Example 296: [Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
Example 297: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
Example 298: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂

- Example 299: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 300: [Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 301: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 302: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- 5 Example 303: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- Example 304: [Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- Example 305: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 306: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 307: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- 10 Example 308: [Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- Example 309: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-decylpiperazine))]hGLP-1(7-36)NH₂
- Example 310: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-dodecylpiperazine))]hGLP-1(7-36)NH₂
- Example 311: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-tetradecylpiperazine))]hGLP-1(7-36)NH₂
- Example 312: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-hexadecylpiperazine))]hGLP-1(7-36)NH₂
- 15 Example 313: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- Example 314: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
- Example 315: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 316: [Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 317: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine))]hGLP-1(7-38)NH₂
- 20 Example 318: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine))]hGLP-1(7-38)NH₂
- Example 319: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine))]hGLP-1(7-38)NH₂
- Example 320: [Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine))]hGLP-1(7-38)NH₂
- Example 321: [Aib^{8,35}, Arg^{26,34}, Glu³⁶(1-dodecylamino)]hGLP-1(7-36)NH₂
- Example 322: [Aib^{8,35}, Glu²⁶(1-dodecylamino), Arg³⁴]hGLP-1(7-36)NH₂
- 25 Example 323: [Aib^{8,35}, Arg²⁶, Glu³⁴(1-dodecylamino)]hGLP-1(7-36)NH₂
- Example 324: [Aib^{8,35,37}, Arg^{26,34}, Glu³⁸(1-dodecylamino)]hGLP-1(7-38)NH₂
- Example 325: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 326: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- 30 Example 327: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 328: [Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂
- Example 329: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

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Example 330: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 331: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 332: [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 333: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 334: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 335: [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 336: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 337: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 338: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 339: [Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 340: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 341: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 342: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 343: [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 344: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 345: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 346: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 347: [Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 348: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

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Example 349: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 350: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

5 Example 351: [Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 352: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

10 Example 353: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 354: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

Example 355: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂

15 Example 356: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 357: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

20 Example 358: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 359: [Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 360: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

25 Example 361: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

Example 362: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

30 Example 363: [Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl))]hGLP-1(7-38)NH₂

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CLAIMS

What is claimed is:

1. A compound of formula (I),
- 5 (R²R³)-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-
A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R¹,
- (I)
- wherein
- A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, or deleted, provided that when A⁷ is Ura, Paa or
- 10 Pta, then R² and R³ are deleted;
- A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;
- A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;
- A¹⁰ is Gly, Acc or Aib;
- A¹¹ is Thr or Ser;
- 15 A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β-Nal, Cha, Trp or X¹-Phe;
- A¹³ is Thr or Ser;
- A¹⁴ is Ser or Aib;
- A¹⁵ is Asp or Glu;
- A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;
- 20 A¹⁷ is Ser or Thr;
- A¹⁸ is Ser or Thr;
- A¹⁹ is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β-Nal or X¹-Phe;
- A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;
- A²¹ is Glu or Asp;
- 25 A²² is Gly, Acc, β-Ala or Aib;
- A²³ is Gln, Asp, Asn or Glu;
- A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;
- A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or
HN-CH((CH₂)_e-X³)-C(O);
- 30 A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);
- A²⁷ is Glu or Asp;
- A²⁸ is Phe, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;
- A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;
- A³⁰ is Ala, Aib or Acc;

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A³¹ is Trp, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe or Ala;

A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu or X¹-Phe;

A³⁴ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

5 A³⁵ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc or a D-amino acid;

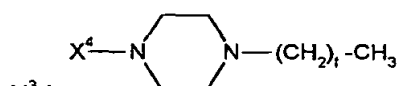
A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

A³⁷ is Gly, β-Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc, Ado, a D-amino acid or deleted;

10 A³⁸ is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

X¹ for each occurrence is independently selected from the group consisting of (C₁-C₆)alkyl, OH and halo;

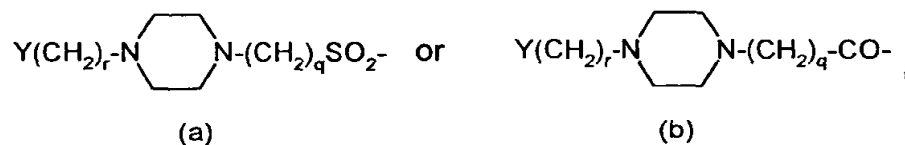
R¹ is OH, NH₂, (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z, wherein X² is a (C₁-C₃₀)hydrocarbon moiety, and Z is H, OH, CO₂H or CONH₂;



X³ is or -C(O)-NHR¹², wherein X⁴ for each occurrence is independently -C(O)-, -NH-C(O)- or -CH₂-, and f for each occurrence is independently an integer from 1 to 29;

each of R² and R³ is, independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and

hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is $(CH_3)_2 - N - \overset{+}{C} = N^-(CH_3)_2$, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, C(O)X⁵,



where Y is H, OH or NH₂; r is 0 to 4; q is 0 to 4; X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl,

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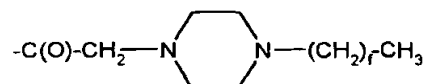
hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl or hydroxynaphthyl(C₁-C₃₀)alkyl;

e for each occurrence is independently an integer from 1 to 4;

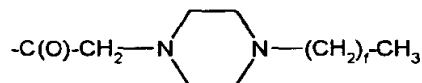
m for each occurrence is independently an integer from 5-24;

5 n for each occurrence is independently an integer from 1-5;

R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



, provided that when R¹⁰ is (C₁-C₃₀)acyl, (C₁-



C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or

, R¹¹ is H or

10 (C₁-C₃₀)alkyl; and

R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;

15 (ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not [Arg^{26,34}, Lys³⁸]hGLP-1(7-38)-E, [Lys²⁶(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys³⁴(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Lys^{26,34}-bis(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E, [Arg²⁶, Lys³⁴(N^ε-alkanoyl)]hGLP-1(8-36, -37 or -38)-E, [Arg^{26,34}, Lys³⁶(N^ε-alkanoyl)]hGLP-1(7-36, -37 or -38)-E or [Arg^{26,34}, Lys³⁸(N^ε-alkanoyl)]hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

(iv) a compound of formula (I) is not Z-hGLP-1(7-36, -37 or -38)-OH, Z-hGLP-1(7-36, -37 or -38)-NH₂, where Z is selected from the group consisting of

25 (a) [Arg²⁶], [Arg³⁴], [Arg^{26,34}], [Lys³⁶], [Arg²⁶, Lys³⁶], [Arg³⁴, Lys³⁶], [D-Lys³⁶], [Arg³⁶], [D-Arg³⁶], [Arg^{26,34}, Lys³⁶] or [Arg^{26,36}, Lys³⁴];

(b) [Asp²¹];

(c) at least one of [Aib⁸], [D-Ala⁸] and [Asp⁹]; and

(d) [Tyr⁷], [N-acyl-His⁷], [N-alkyl-His⁷], [N-acyl-D-His⁷] or [N-alkyl-D-His⁷];

30 (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

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(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36 or -37), [Glu¹⁵]hGLP-1(7-36 or -37), [Asp²¹]hGLP-1(7-36 or -37) or [Phe³¹]hGLP-1(7-36 or -37).

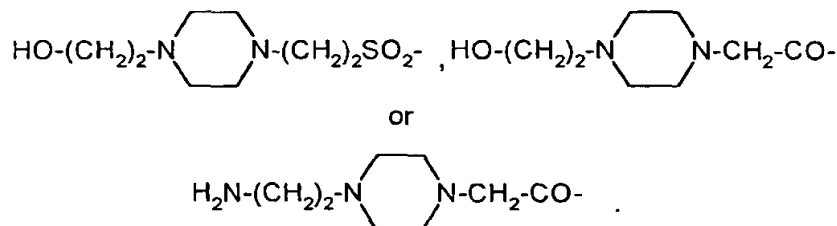
2. A compound according to claim 1, wherein A¹¹ is Thr; A¹³ is Thr; A¹⁵ is Asp; A¹⁷ is Ser; A¹⁸ is Ser; A²¹ is Glu; A²³ is Gln or Glu; A²⁷ is Glu; and A³¹ is Trp; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, Acc or Aib; A¹⁹ is Tyr; A²⁰ is Leu, Acc or Cha; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_n-X³)-C(O); A²⁸ is Phe; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val or Acc; or a pharmaceutically acceptable salt thereof.

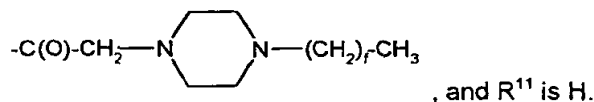
4. A compound according to claim 3, wherein A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β-Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β-Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β-Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R¹ is OH or NH₂.

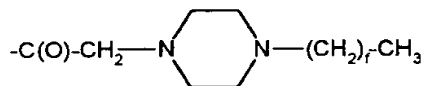
6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,



7. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl or



8. A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₄-C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or



9. A compound according to claim 1 wherein said compound is

- 5 [Aib^{8,35}]hGLP-1(7-36)NH₂,
 [(N^α-HEPES-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
 [(N^α-HEPA-His)⁷, Aib^{8,35}]hGLP-1(7-36)NH₂,
 [Aib⁸, β-Ala³⁵]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 10 [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-dodecanesulfonyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl))]hGLP-1(7-36)NH₂,
 15 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine))]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino)]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH or
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl)]hGLP-1(7-36)-OH, or a pharmaceutically acceptable salt thereof.

20 10. A compound according to claim 9 wherein said compound is

- [Aib^{8,35}]hGLP-1(7-36)NH₂,
 [Aib⁸, β-Ala³⁶]hGLP-1(7-36)NH₂,
 [Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl)]hGLP-1(7-36)NH₂,
 [Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl)]hGLP-1(7-38)NH₂,
 25 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl)]hGLP-1(7-36)NH₂, or
 [Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷]hGLP-1(7-37)-OH, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

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12. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

13. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

14. A method according to claim 13 wherein said disease is Type I diabetes or Type II diabetes.

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ABSTRACT

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

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Docket No.
BPC089

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ANALOGUES OF GLP-1

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

_____	_____
(Application Serial No.)	(Filing Date)
_____	_____
(Application Serial No.)	(Filing Date)
_____	_____
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

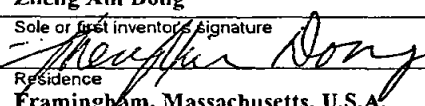
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